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Cerebral Palsy Genetics: Who to Test?

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Abstract

AIM: To determine which cerebral palsy (CP) patients should undergo genetic testing, we compared the rate of likely causative genetic variants from whole exome sequencing (WES) in individuals with and without environmental risk factors. We hypothesized that the rate of causative variants would be higher in individuals without risk factors for CP.

METHOD: Patients were recruited from a single academic medical center, and research WES was completed. Participants were evaluated for the following risk factors: prematurity, brain bleed or stroke, birth asphyxia, brain malformations, and intrauterine infection.

RESULTS: A total of 150 unrelated individuals with CP participated. Causative genetic variants were identified in 14 participants (9.33%). There was no significant difference in diagnostic rate between individuals with CP risk factors (10/122; 8.20%) compared with individuals without risk factors (4/28; 14.3%); Fisher's exact p=0.298.

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Web resources:
Analysis Tool for Annotated Variants (ATAV): https://redmine.igm.cumc.columbia.edu/projects/atav/wiki
ClinVar browser: http://www.ncbi.nlm.nih.gov/clinvar/
Consensus Coding Sequence (CCDS), https://www.ncbi.nlm.nih.gov/CCDS/
ExAC Browser: http://exac.broadinstitute.org/
Ensembl genome assembly GRCh37: http://grch37.ensembl.org/Homo_sapiens/Info/Index
Ensembl Variant Effect Predictor (VEP): http://grch37.ensembl.org/Homo_sapiens/Tools/VEP
gnomAD browser: https://gnomad.broadinstitute.org/
NHLBI Exome Sequencing Project (ESP) Exome Variant Server: http://evs.gs.washington.edu/EVS/
OMIM: http://www.omim.org/
Pubmed: https://www.ncbi.nlm.nih.gov/pubmed
The Human Gene Mutation Database (HGMD): http://www.hgmd.cf.ac.uk/ac/index.php

INTERPRETATION: While the rate of genetic diagnoses among individuals without risk factors is almost double the rate of those with risk factors, the difference is not statistically significant at this sample size. The identification of genetic diagnoses in over 8% of cases with risk factors suggests that these might confer susceptibility to environmental factors, and that further research should include individuals with risk factors.

Background

Cerebral palsy (CP) describes a group of permanent disorders of movement causing activity limitation that are attributed to nonprogressive disturbances in the developing fetal or infant brain (1,2). CP remains the most common motor disability in childhood with an estimated frequency of 2 per 1,000 live births (3). CP was historically considered an acquired condition, attributed to environmental factors such as infection, neonatal stroke, and birth asphyxia. However, as many as 10-15% of individuals with CP do not have a clear etiology. Given the heterogeneity of causes within the “cerebral palsies” (4-8), it is likely that genetics plays a role, but how large a role and which populations might be most affected is not well understood.

Several collaborations have sought to find genetic variants in different populations of people with CP (9-13). While some groups have included all participants with CP, others have targeted specific phenotypes such as hemiplegic or ataxic CP compared to unrelated controls (12,14). While most published studies proposing pathogenic gene variants as a CP etiology are case reports or small series, larger studies employ standardized prospective testing such as microarray, exome and transcriptome methodology. Altogether, studies reporting *de novo* and inherited genetic variants continue to expand the ever-growing list of “CP genes” (10,15-23) (See Table 2). Interestingly, many of these research papers also noted potential environmental risk factors in even those individuals with identified pathogenic genetic variants, and support an important interaction between risk genes and environmental insults leading to the CP condition proposed by Fahey et al (6).

Despite the ever-growing list of CP genes, there is no standardized approach to genetic testing in CP patients. The International Cerebral Palsy Genomics Consortium (ICPGC) aims to align experts in this field with the goal of establishing evidence-based recommendations about genetic testing in individuals with CP (24). There remains a gap in our understanding about which people with CP should be tested, and specifically whether CP risk factors alter the likelihood of identifying a causative genetic variant in some individuals. For this project, we hypothesized that people without known CP risk factors would have a higher rate of causative genetic variants. We tested this hypothesis by performing whole exome sequencing in an unselected group of people with CP and determining the rate of causative variants in people with and without known risk factors. Secondary analyses were subsequently performed to determine associations between patient characteristics and diagnostic rates.

Methods

Participants were recruited in the Weinberg Family Cerebral Palsy Center (WFCPC) and in various clinics across New York Presbyterian Hospital/Columbia University Irving Medical Center (NYP/CUIMC) between 2015 and 2020. In 2020, enrollment stopped due to the COVID-19 pandemic. The WFCPC treats people of all ages with CP through multidisciplinary care in orthopedics, neurology, and rehabilitation medicine. Participants were referred by physicians in the WFCPC, and interested participants were enrolled by the research coordinator. The majority of participants outside of the WFCPC were referred by physicians from the clinical genetics and neurology clinics. Interested participants were enrolled by a research genetic counselor. Written informed consent for all participants was obtained through an institutional review board-approved research study at the Institute for Genomic Medicine (IGM) at Columbia University (protocol AAAO8410). Trio or non-trio whole exome sequencing (WES) analysis was completed depending on parents' availability.

The inclusion criterion was a clinical diagnosis of CP, and there were no exclusion criteria. Through examination of the medical record and interviews with the individuals and family members, we screened for the following six risk factors: prematurity (born <32 weeks gestational age), intraventricular hemorrhage or stroke, intrauterine infection, major brain malformations, birth asphyxia, or other identified environmental risk factors. Participants returned to the clinic for further investigation if there were questions or concerns about characterization of phenotype after WES analysis.

DNA was extracted from maternal, paternal, and proband samples, exome sequenced on a HiSeq 2500 or NovaSeq 6000 with the Kapa Biosystem's Library Preparation Kit, and whole-exome captured with NimbleGen SeqCap EZ v.3.0 rapid or v.4.

Sequence data were analyzed with an updated version of our established trio sequencing framework (**Figure 1**) (25), which identifies "qualifying" genotypes not observed in the parents, 18,746 internal control individuals, or two external databases of 6,503 and 60,706 control individuals provided by the National Heart, Lung, and Blood Institute (NHLBI) Exome Sequencing Project (ESP6500SI [March 2013 release]) and the Exome Aggregation Consortium (ExAC Browser v.0.3 [January 2015 release]), respectively. We further searched for variants in previously reported CP genes based on literature review (10,15-23) (Table S1). Qualifying genotypes and CP gene variants underwent manual curation by a research genetic counselor. Variants were assessed for genotype-phenotype correlation and possible disease mechanism by literature review. Candidate genotypes were further reviewed by the wider research team, which included bioinformaticians, neurologists and geneticists, to reach a consensus interpretation. Time between enrollment and the date of the results discussion for each participant averaged 5 months and 12 days. Criteria for variants likely to be confirmed included loss-of-function (LoF) variants in genes intolerant to LoF changes, missense variants that have been clearly previously reported as pathogenic, de novo missense variants in genes intolerant to missense changes, and homozygous or compound heterozygous (CHET) variants if both variants are previously reported or have a LoF disease mechanism. Variants deemed causative were confirmed in a clinical laboratory improvement amendment (CLIA) certified laboratory and interpreted according to American College of

Medical Genetics and Genomics (ACMGG) guidelines (26) and returned to patients and their referring provider. Incidental findings from the ACMGG recommended list (26,27) were not routinely evaluated and were only reported to the parents if they emerged through our trio analysis framework.

The significance of difference in diagnostic rate between individuals with and without risk factors for their CP was calculated using Fisher's exact. Secondary analyses to determine correlations between patient comorbidities and diagnostic rates were evaluated by performing enrichment analysis and multivariate regression to evaluate any predictors of a positive genetic diagnosis based on participant comorbidities. We performed logistic regression on phenotypic descriptors to predict whether the probands had a genetic diagnosis, and compared the classifier's weights for these descriptors.

Results

A total of 150 unrelated individuals with CP were included in our cohort; the age, sex, gross motor function classification system (GMFCS) level (28), body part affected, number of family members sequenced, and site of recruitment are shown in Table 1. Of the 150 participants in our cohort, 96 were recruited and enrolled by research coordinators in the WFCPC, and 54 were recruited and enrolled by research genetic counselors in the clinical genetics and neurology clinics at NYP/CUIMC. A total of 739 patients with CP had appointments at the WFCPC and were potentially eligible for enrollment into the study. Of the 739 potentially eligible patients, 244 were approached by study coordinators. The 495 patients who were potentially eligible but did not meet with a study coordinator had varying conflicts including shortage of time, appointment cancellations or no-shows, or off-site appointments. Patients who met with a study coordinator but decided not to enroll had time conflicts or were disinterested in the study. Out of the 150 cases, a total of 8 cases required an additional research phenotype visit to better understand their phenotype and CP diagnosis. Across the 150 cases, 122 (81.3%) had identified risk factors associated with their CP and 28 (18.7%) had no identified risk factors.

Sequencing of the exomes produced 786 (SD 34) variants per case. These bioinformatics filters resulted in ~5-25 prioritized variants per case requiring manual curation. Focusing on the CP gene list analysis, our 150 probands had 900 variants within 111 CP-associated genes (10,15-23), listed in Table S.2 The majority of these variants occurred frequently within the population (5 or more alleles in gnomAD) or were inherited from unaffected parents, suggesting they are unlikely to be causal for CP in these probands. Only 148 (16.4%) of these "CP-specific" candidate variants were not inherited and occurred in the Genome Aggregation Database (gnomAD) fewer than 5 times. Although these 148 variants are interesting candidates for additional investigation, none of the variants established a diagnosis that was missed through the standard IGM analysis.

A total of 14 causative genetic variants were returned to participants of the study. There was no significant difference in diagnostic rate between individuals with identified CP risk factors (10/122; 8.20%) compared with individuals without identified CP risk factors (4/28; 14.3%); Fisher's exact p=0.298. Table 2 shows details of the genetic variants, ACMGG

classifications as determined by the clinical lab, and a brief description of participants' phenotypes and any known risk factors. Genetic findings among the cohort without risk factors included variants in the *SPAST* (MIM: 604277), *L1CAM* (MIM: 308840), and *PPT1* (MIM: 600722), genes, and among the cohort with risk factors were variants in the *ATM* (MIM: 607585), *SMARCB1* (MIM: 601607), *ZSWIM6* (MIM: 615951), *GNAO1* (MIM: 139311), *MECP2* (MIM: 300005), *PANK2* (MIM: 606157), *SCN1A* (MIM: 182389), *COL4A1* (MIM: 120130), and *DOCK6* (MIM: 614194) genes. Variants in the *SCN2A* (MIM: 182390) gene were reported in patients both with and without identified risk factors. Six of the variants were in genes not previously associated with CP, but were associated with other developmental disorders but not CP (*ATM, SMARCB1, ZSWIM6, PPT1, SCN1A*, and *DOCK6*). There were no ancillary diagnoses made in parents of participants who had clinically confirmed likely causative genetic variants.

Many participants had comorbidities in addition to CP including but not limited to other diagnoses related to the nervous system, epilepsy, and global developmental delay / intellectual disability (GDD/ID). A complete list of participant clinical information is provided in Table S.1. We trained a logistic regression classifier on 15 phenotypic descriptors including: prematurity, age, spastic CP, hemiplegic CP, dystonic CP, diplegic CP, quadriplegic CP, GDD/ID, epilepsy, seizures, other neuro phenotype, metabolic/GI issues, hypothyroidism, cardiac/stroke, and whether the CP was considered to have a known cause to predict whether a proband would obtain a positive genetic diagnosis. The presence of GDD/ID was the strongest predictor of a positive genetic diagnosis, achieving a high positive weight within the trained classifier. Among these phenotypic descriptors, GDD/ID was found in 12/14 of probands with genetic diagnoses compared to 76/150 in the entire cohort. This association (Fisher's exact p-value = 0.00931) was not significant when corrected for multiple comparisons (Bonferroni corrected p-value threshold of 0.00333). History of prematurity and history of intraventricular hemorrhage were among the strongest predictors of a negative case (largest negative weight in the trained classifier). Trio analysis was another predictor of a positive genetic testing result, with a diagnostic yield for trio analysis (12/46; 26.1%) significantly higher compared to non-trios (2/104; 1.92%) trios had a higher diagnostic yield than non-trios; Fisher's exact $p=1.22e^{-5}$.

Discussion

While the rate of genetic diagnoses among individuals without risk factors is almost double the rate of those with risk factors (14.3% versus 8.20%), at this sample size the difference is not statistically significant as our cohort was disproportionately made up of participants with environmental risk factors. This difference may reach significance with expanded cohort sizes. However, regardless of difference in diagnostic rate, we found a compelling portion of individuals with both causative genetic variants and environmental risk factors. There are several possible reasons for this. First, there may be a genetic susceptibility to the damaging effects of environmental insults. That is, the same environmental stress produces greater injury because of the genetic variant. Alternatively, the genetic variants may predispose to the risk factors of prematurity, infection, or others; having the variant would make the likelihood of these risk factors greater as proposed by Fahey et al (6). These diagnoses suggest that genetics may still play an important role in CP even in cases with known

environmental risk factors, and that future genetic research should continue to include such cases in order to better understand the role of genetic and environmental contributors.

The IGM's standard analysis, which uses a phenotype-agnostic approach to identify qualifying genotypes for manual curation and subsequent phenotype correlation, identified six causative variants in genes not previously associated with CP. The *ATM, SMARCB1, ZSWIM6, SCN1A, DOCK6*, and *PPT1* genes are associated with developmental disorders that include symptoms such as ataxia, difficulty walking, chorea, myoclonus, movement abnormalities, limb malformations, epilepsy, developmental disability, autism and/or dysmorphic facial features (29-31), but have not been previously reported as associated with CP. *SCN1A*, a well-described epilepsy gene, was identified in a patient with quadriplegic cerebral palsy, epilepsy, static encephalopathy, and global developmental delay. Individuals with pathogenic variants in *SCN1A* often develop a crouched gait, and can progress with decreased passive knee extension, increased external tibial torsion, and pes planovalgus (30). In addition to the expanding phenotype of *SCN1A*-related disorders, there is evidence of genotype-phenotype correlation between different variants in the *SCN1A* gene (31), and that genetic modifiers may contribute to the variable manifestation of patients with *SCN1A* mutations (32,33). Although this gene is likely causative of the patient's epilepsy, it is unclear if it explains his/her CP phenotype. Five of the six causative variants in genes not previously associated with CP were in patients with risk factors.

We identified eight causative variants in known CP risk genes including *GNAO1, MECP2, PANK2, SCN2A, COL4A1, SPAST*, and *L1CAM* (10,15-18,21,34,35). *MECP2, PANK2, SCN2A*, and *COL4A1* are also associated with progressive disorders of movement, epilepsy, autism, infantile hemiplegia, and brain bleeds (15,17,21,35). These variants were subsequently confirmed, classified and returned by a clinical lab. *SPAST* and *L1CAM* have strong associations with CP and cause progressive disorders of the nervous system (10,15-18,34). Six of eight of the causative variants in genes previously associated with CP were in patients with risk factors. Variants in the *SCN2A* gene were reported in patients both with and without identified risk factors, and are considered to fully explain the phenotypes in both patients.

The prevalence of diagnoses in genes without any previous associations with CP suggests there are more single-gene etiologies for CP that are yet to be discovered, emphasizing the importance of genetic analysis beyond currently-known CP genes. The diagnoses of individuals with a CP phenotype with underlying genetic syndromes has the potential to change the clinician's thought process when gathering evidence to understand the etiology of CP, as well as the defined symptoms and conditions known to be associated with known genetic syndromes. There is a lot of research to be done to understand the phenotype-genotype correlations between the genes causing these 'known' genetic syndromes, whose definitions may be expanded to include CP. The diagnoses of individuals with a CP phenotype with underlying genetic syndromes also suggests that testing for more genes than are currently associated with CP may be warranted.

In addition to the genetic diagnoses, we identified seven strong candidate variants which do not meet criteria for pathogenicity at this time but may warrant further follow-up. Six of

the seven candidate variants in genes with no current disease association were in patients with identified risk factors. Given the rate of patients in our cohort in which we identified genetic diagnoses or strong candidate variants who had previously identified risk factors for CP, our data suggests that individuals both with and without identified risk factors for CP benefit from genetic testing. It is still unknown whether these underlying genetic diagnoses or the environmental exposures these individuals experienced caused their CP. The genetic contributions identified may be a direct effect on the nervous system, or a susceptibility to environmental effects.

Global developmental delay and intellectual disability were associated with a positive genetic diagnosis across the entire cohort, suggesting that abnormalities in movement and cognitive domains may confer a higher probability of a genetic cause. In addition, many positive cases had other associated conditions such as epilepsy and other specific movement disorders. Important examples include a participant with a causative variant in *SMARCB1* causing Coffin-Siris Syndrome, who presented with CP, cortical visual impairment, nystagmus, strabismus, developmental delay, duplicated right collecting system with mild right hydronephrosis, sensorineural hearing loss, short stature, and scoliosis. Another example is a participant with a causative variant in *L1CAM*, who presented with diplegic CP, developmental delay, and a history of hydrocephalus. A final example is a participant with a causative variant in *ZSWIM6*, who presented with spastic hemiplegic CP, developmental delays, autism, intraventricular hemorrhage/stroke, and ADHD. A complete list of participant clinical information is provided in Table S.1. By proactively taking a thorough medical history and documenting it in the patient's record, clinicians can give a full representation of the patient's medical history and help genetic testing labs interpret the patient's DNA.

There are a number of limitations of this study. First, the small sample size of participants was insufficient to provide a robust predictive model, and future studies with larger sample sizes are needed to better evaluate the difference in genetic testing diagnostic rates between participants with and without identified risk factors for CP. Second, WES was the only genetic testing performed in this study. It is difficult to compare findings from this study with that of other studies in which participants have had whole genome sequencing (WGS) or copy number variant analysis. It is possible some diagnoses were missed by not performing these additional genetic tests. Third, the genetic variant analysis process was designed to identify single-gene causes of genetic conditions; low-risk susceptibility genes and multigenic causes would not be identified through this analysis. Fourth, the phenotyping portion was largely retrospective: we used the medical record to understand the risk factors associated with participants' CP with supplemental follow up visits as needed. Prospective analysis may have identified other risk factors.

In conclusion, our results showed no significant difference in diagnostic rate in individuals with and without risk factors for CP, and the majority of individuals with genetic diagnoses had previously identified risk factors. Future studies are needed to determine the pre-test probability of genetic diagnosis based on etiology, comorbidities, and body part affected. Other variables, such as how actionable the diagnoses are, the cost of testing, and the risk of

returning unrelated genetic variants will further help to define which people with CP should undergo genetic testing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What this paper adds:

- No significant difference in diagnostic rate between individuals with/without risk factors
- Genetic variants may confer susceptibility to environmental risk factors
- Six causative variants identified in genes not previously associated with CP
- Global developmental delay and intellectual disability associated with positive genetic diagnoses

Table 1.

Demographics and Recruitment of CP Participants

Total Participants[1]	**N= 152**
Age	25 (SD 17.36)
Mean age	25 years 7 months
Overall Median Age	27.613
Median Age for Positive Cases	13.324
Sex	
Females	N=81
Males	N=71
GMFCS[2] **Scores**	
I:	28%
II:	27%
III:	25%
IV:	7%
V:	13%
Body Part Affected	
Spastic diplegic	30.3%
Spastic quadriplegic	32.9%
Spastic hemiplegic	32.9%
Athetoid CP	3.95%
Family Type Completed	
1. Proband Only	40.1%
2. Trios (proband + 2 parents)	29.0%
3. Duos (proband + 1 parent)	27.6%
4. Quad (Proband + 2 parents + 1 sibling)	2.63%
5. Treble (Proband + 1 parent + 1 sibling)	0.658%
Etiology	
Identified Risk Factor	**81.6%**
1. ***Prematurity (PM)***	28.3%
• PM & Intraventricular hemorrhage/stroke (IHS)	5.90%
• PM & IHS, birth asphyxia (BA)	1.32%
• PM & BA	8.55%
2. ***IHS***	18.4%
• IHS & BA	4.61%
3. BA	11.8%
4. Intrauterine Infection	2.63%
No Identified Risk Factor	18.4%
Site of Recruitment	
1. Children Hospital (Orthopedics)	63.2%
2. Genetics	18.4%

Total Participants[1]	**N= 152**
3. Neurology	11.8%
4. Pediatric Neurology	3.95%
5. Pediatric Intensive Care	2.63%

[1] N includes two affected siblings enrolled in the study (not included in diagnostic rate)

[2] GMFCS; gross motor function classification system

Table 2.

Genetic Variants Identified in CP Patients.

Gene	Age	Risk Factor	Clinical Description	GMFCS	Genomic coordinate (hg19)	Nucleotide change, amino acid change	RefSeq Identifier	Clinical Classification	Inheritance	Zygosity
SPAST (MIM: 604277)	10	N/A	Spastic quadriplegia	Between 3-4	2:32361636	c.1251_1253delAGA, p.Glu418del	NM_001363823.2	LP[a]	DN[b]	Het[c]
L1CAM (MIM: 308840)	13	N/A	Diplegic CP	3+	X:153134145	c.1417C>T, p.Arg473Cys	NM_001143963.2	LP[a]	Maternal	Het[c]
ATM (MIM: 607585)	6	Intraventricular stroke	Quadriplegic CP	Unknown	11:108115754 and 11:108196890	c.901+1G>A and c.6916_6917del, n/a and p.Leu2307CysfsTer 65	NM_001351834.2	P[d], P (CHET)[e]	Paternal, Maternal	CHET[e]
SCN2A (MIM: 182390)	13	N/A	Spastic CP, epilepsy	Unknown	2:166165896	c.640T>C, p.Ser214Pro	NM_001040142.2	LP[a]	DN[b]	Het[c]
SMARCB1 (MIM: 601607)	10	Prematurity, birth asphyxia	Spastic CP	Unknown	22:24176330	c.1121G>A, p.Arg374Gln	NM_003073.5	LP[a]	DN[b], HZE[f]	Het[c]
ZSWIM6 (MIM: 615951)	5	Intraventricular hemorrhage/ stroke	Spastic hemiplegic CP	Unknown	5:60817195	c.1439G>A, p.Trp480Ter	NM_020928.2	VOUS[g]	Unknown	Het[c]
PPT1 (MIM: 600722)	4	N/A	Quadriplegic CP	Unknown	1:40562790	c.115_120del, p.His39_Gly40del	NM_000310.4	LP[a]	Paternal, Maternal	Hom[h]
SCN2A (MIM: 182390)	5	Intraventricular hemorrhage	Spastic quadriplegic CP	Unknown	2:166198955	c.2538G>T, p.Leu846Phe	NM_001040143.2	LP[a]	DN[b]	Het[c]
GNAO1 (MIM: 139311)	15	Intraventricular hemorrhage, birth asphyxia	Right side hemiparesis, spasticity, dystonia	Unknown	16:56370711	c.662C>A, p.Ala221Asp	NM_138736.3	LP[a]	DN[b]	Het[c]
MECP2 (MIM: 300005)	1	Birth asphyxia	Generalized hypotonia, spasticity	Unknown	X:153297682	c.353G>A p.Gly118Glu	NM_001110792.2	VOUS[g]	Hem[i]	Het[c]
PANK2 (MIM: 606157)	19	Birth Asphyxia	Generalized dystonia & spastic quadriplegia CP	Unknown	20:3893282	c.1412+1G>C, n/a	NM_153638.3	LP[a]	Paternal, Maternal	Hom[h]
SCN1A (MIM: 182389)	14	Birth asphyxia, intraventricular stroke/ hemorrhage	Spastic quadriplegic CP	Unknown	2;166895942	c.2492_2495delGTTC, p.R830Hfs	NM_006920.6	P[d]	Evidence of parental mosaicism	Het[c]
COL4A1 (MIM: 120130)	11	Birth asphyxia	Spastic quadriparesis, left-sided hemiparesis	Unknown	13:110831699	c.2263G>A, p.G755R	NM_001845.6	P[d]	DN[b]	Het[c]

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Gene	Age	Risk Factor	Clinical Description	GMFCS	Genomic coordinate (hg19)	Nucleotide change, amino acid change	RefSeq Identifier	Clinical Classification	Inheritance	Zygosity
DOCK6 (MIM: 614194)	1	Periventricular Stroke	Spasticity, chronic mild left hemiparesis and right hypotonia	Unknown	19:11338160	c.2815-7C>G, n/a	NM_020812.4	VOUS[g]	Paternal, Maternal	Hom[h]
COL12A1 (MIM: 120320)	40	Prematurity	Spastic quadriplegic CP	3	6:75855961	c.4418-1G>A, n/a	NM_004370.6	n/a	Unknown	Het[c]
GARS1 (MIM: 600287)	30	Birth asphyxia	Quadriplegic CP; dystonic CP	2	7:30671863	c.1904C>T, p.Ser635Leu	NM_002047.4	n/a	Maternal	Het[c]
ABCD1 (MIM: 300371)	42	Prematurity, birth asphyxia	Spastic hemiplegic CP-right hand dominant	2	X:152991545	c.824G>A, p.Arg275Gln	NM_000033.4	n/a	Unknown	Het[c]
MFN2 (MIM: 608507)	42	Prematurity, birth asphyxia	Spastic hemiplegic CP-right hand dominant	2	1:12069698	c.2119C>T, p.Arg707Trp	NM_001127660.1	n/a	Unknown	Het[c]
TENM4 (MIM: 610084)	27	Prematurity	Left hemiplegic CP	1	11:78565260	c.1569delC, p.Ser524ProfsTer85	NM_001098816.3	n/a	Unknown	Het[c]
ZFHX3 (MIM: 104155)	38	N/A	Dystonic CP	2	16:72828504	c.8077C>T, p.Arg2693Ter	NM_006885.4	n/a	Unknown	Het[c]
CSMD1 (MIM: 608397)	28	Prematurity	Spastic diplegic CP	2	8:3566014	c.932-1G>C, n/a	NM_033225.6	n/a	Unknown	Het[c]

LP[a]; likely pathogenic, DN[b]; de novo, Het[c]; heterozygous, P[d]; pathogenic, CHET[e]; compound heterozygous, HZE[f]; hotzone essential, VOUS[g]; variant of unknown significance, Hom[h]; homozygous, Hem[i]; hemizygous